



## Evidence-based Practice Center Systematic Review Protocol

Project Title: Effects of Dietary Sodium and Potassium Intake on Chronic Disease Outcomes and Related Risk Factors

Initial publication date if applicable:

Amendment Date(s) if applicable:

(Amendments Details—see Section VII)

### I. Background and Objectives for the Systematic Review

The Governments of the United States and Canada have jointly undertaken the development of the Dietary Reference Intakes (DRIs) since the mid-1990s. Federal DRI committees from each country work collaboratively to identify DRI needs, prioritize nutrient reviews, and advance work to resolve any methodological issues that could impede new reviews. The commission of a systematic review for nutrients under review is now an integral part of the DRI process. Recently the DRI Working Group recommended that a sodium and potassium evidence review be conducted to inform the update of the sodium and potassium DRIs by the Institute of Medicine (Health and Medicine Division [HMD] of the National Academies of Sciences, Engineering, and Medicine).

DRIs are a set of reference values that provide guidance on adequate and safe intakes of nutrients across the life span, by sex, and during pregnancy and lactation in apparently healthy individuals. They are based on an expert consensus process in which ad hoc committees convened by the Food and Nutrition Board of the HMD used scientific evidence, augmented by scientific judgment when dealing with uncertainties, to derive the reference values. The default reference values for adequate intakes are Estimated Average Requirements (EARs), from which a Recommended Daily Allowance (RDA) is derived, “the average daily intake level sufficient to meet the nutrient requirement of nearly all healthy individuals” (97.5 percent) in a particular age and sex (life stage) group. If the available data are inadequate to identify an RDA requirement for nutrient sufficiency, an Adequate Intake (AI) reference value may be used in place of an EAR/RDA. The reference value that represents an intake above which the risk of potential adverse effects due to excessive intakes may increase is called the Tolerable Upper Intake Level (UL).

The DRIs are for dietary intakes only (i.e., foods and dietary supplements) and are intended to cover the needs of almost all healthy persons. These values serve multiple purposes, including guidance for a) health professionals for use in dietary counseling and for developing educational materials for consumers and patients, b) scientists in designing and interpreting research, c) users of national nutrition monitoring, and d) policy for a number of applications such as the Dietary Guidelines for Americans, nutrition labeling, and federal nutrition programs.

The process of deriving nutrient reference values by an ad hoc expert Committee involves a series of decisions that need to be informed by available evidence. The Committee often used the same studies to answer different questions, although the relevance of different types of information from available studies may vary from question to question. Therefore, these systematic reviews need to anticipate the full range of information needed as the Committee works through their series of questions.

In 2005, the Dietary Reference Intakes: Water, Potassium, Sodium, Chloride, and Sulfate report was released by the Institute of Medicine Food and Nutrition Board.<sup>1</sup> The report established nutrient reference values for water, potassium, sodium, chloride and sulfate to maintain health and reduce chronic disease risk.

The AI is a recommended intake level thought to meet or exceed the nutrient requirements of almost all individuals in a particular life stage and gender group.<sup>2</sup> The 2005 IOM report set the AI for sodium for the population aged 19-50 years at 1500 mg per day based on three criteria: 1) meeting the need for all essential nutrients 2) covering sodium sweat losses in un-acclimatized individuals who are exposed to high temperatures or who are moderately physically active (as recommended in other DRI reports) and 3) exceeding the level of sodium intake associated in some studies with adverse effects on blood lipids and insulin resistance. The AI does not apply to highly active populations such as competitive athletes and workers exposed to extreme heat stress, such as fire fighters.<sup>1</sup>

The critical endpoint selected for determination of the Tolerable Upper Intake Level (UL) was blood pressure.<sup>2</sup> The IOM concluded that the relationship between sodium intake and blood pressure was continuous without an apparent threshold and thus it was difficult to precisely set a UL, especially because other factors (weight, exercise, potassium intake, dietary pattern, alcohol intake, and genetic factors) also affect blood pressure. The IOM set the UL for sodium at 2,300 mg per day for people aged 14 years and over, with lower values for those 1-13 years of age. In dose-response trials, this level was commonly the next level above the AI that was tested. The ULs for children were extrapolated from the adult UL based on median energy intakes. It should be noted that the UL is not a recommended intake and, as with other ULs, there is no benefit to consuming levels above the AI.<sup>1</sup>

Since 2005, two related IOM reports, Strategies to Reduce Sodium Intake in the United States<sup>3</sup> and Sodium Intake in Populations: Assessment of Evidence<sup>4</sup> have been published. The literature summarized in the reports supported efforts to reduced sodium intake to less than 2,300 mg per day and provided guidance on future research needs. A number of additional evidence reviews, including the NHLBI-funded evidence review which included sodium and potassium, Lifestyle Interventions to Reduce Cardiovascular Risk,<sup>5</sup> and three Dietary Guidelines for Americans reports have been published, the most recent one being the 2015-2020 Dietary Guidelines for Americans.<sup>6</sup>

The relationship between sodium intake and blood pressure is well established based on a diverse body of evidence including clinical trials. Recent pooled studies from randomized controlled trials show that reducing sodium leads to reductions in blood pressure among people with and without high blood pressure.<sup>6-10</sup> The Lifestyle report concluded that there is strong evidence that reducing sodium intake lowers blood pressure.<sup>5</sup> Additionally

evidence has shown that higher dietary sodium intake is associated with greater risk for fatal and nonfatal stroke and cardiovascular disease.<sup>4, 6, 7, 11</sup> Since high blood pressure is strongly associated with a higher risk for CVD, stroke, congestive heart failure, and kidney disease and lowering blood pressure lowers these risks, an indirect relationship between sodium intake and CVD is assumed.<sup>12-14</sup> Given the shift to assessing the direct relationship between nutrient intake and chronic disease outcomes (CVD, Stroke, MI, etc.), the findings from observational studies have been subjected to greater scrutiny and have generated more controversy. The limitations of some of these studies related to sodium intake and CVD outcomes have been carefully reviewed and critiqued.<sup>15</sup> Limitations may include methods used for sodium intake assessment, residual confounding, and possible reverse causality.

The 2005 IOM committee also set an AI level for potassium at 4,700 milligrams per day, based on levels that blunt the sodium-related increase in blood pressure as well as the reduction in risk of kidney stones.<sup>1</sup> The DRI report noted the need for dose-response studies on potassium related to cardiovascular disease and blood pressure. The IOM Sodium Intake in Populations report listed “analyses examining the effects of dietary sodium in combination with other electrolytes, particularly potassium” on health outcomes as a research gap.<sup>4</sup> Understanding the health effects of potassium added to the diet and interaction of potassium with sodium are essential. The latter is particularly important in monitoring the health impact of the use of potassium chloride (KCL) as a salt substitute in reformulating foods to reduce the amount of sodium, as KCL is already in use as a salt substitute in foods, including selected restaurant and packaged foods.

The DRI steering committees jointly decided that prior to undertaking a nutrient review, whether—and how—data on chronic disease risk reduction could be used in setting DRI values need to be determined. Thus, a scientific expert panel was convened to review and critically evaluate evidentiary, dose response, and process issues related to the use of chronic disease endpoints and develop options for their incorporation into future DRI reviews.<sup>16</sup> A panel report has been accepted for publication in the American Journal of Clinical Nutrition. Because chronic disease endpoints were essential to development of the current UL for sodium, 2,300 milligrams per day, and may be used to set other DRI values, the US and Canadian steering committees commissioned the HMD to develop an authoritative report on the feasibility and practicality of using chronic disease endpoints in setting DRI values, and to develop an appropriate framework for use by future DRI panels.

This review will focus on sodium and potassium intake, chronic disease risk reduction and related outcomes in the questions below. The goal of this review is to provide a future DRI sodium and potassium panel with a systematic review of the evidence on key questions that includes the general body of evidence reviewed by the 2005 DRI panel<sup>1</sup> (through 2002) and updated evidence.

## II. The Key Questions

The review aims to answer eight key questions (KQs), formulated by federal sponsors of the review. Four KQs address sodium intake and four address potassium intake. Four KQs address the effect of interventions evaluated in RCTs and four the associations found in observational studies. KQ2 was modified to include adults as well as children.

## Sodium

1. Among adults and children of all age groups (including both sexes and pregnant and lactating women), what is the **effect** (benefits and harms) of interventions to reduce dietary sodium intake on blood pressure at the time of the study and in later life?
  - a. Do other minerals (e.g., potassium, calcium, magnesium) modify the effect of sodium?
  - b. Among subpopulations defined by sex, race/ethnicity, age (children, adolescents, young adults, older adults, elderly), and for women (pregnancy and lactation).
  - c. Among subpopulations defined by hypertension, diabetes, and obesity health status.
2. Among adults and children, what is the **association** between dietary sodium intake and blood pressure?
  - a. Among subpopulations defined by sex, race/ethnicity and age (children, adolescents, young adults, older adults, elderly).
  - b. Among subpopulations defined by hypertension, diabetes, and obesity health status.
3. Among adults, what is the **effect** (benefits and harms) of interventions to reduce dietary sodium intake on CVD and kidney disease morbidity and mortality and on total mortality?
  - a. Do other minerals (e.g., potassium, calcium, magnesium) modify the effect of sodium?
  - b. Among subpopulations defined by sex, race/ethnicity, age (adults, older adults, elderly), and for women (pregnancy and lactation).
  - c. Among subpopulations defined by hypertension, diabetes, obesity and renal health status.
4. Among adults, what is the **association** between dietary sodium intake and CVD, CHD, stroke and kidney disease morbidity and mortality and between dietary sodium intake and total mortality?
  - a. Do other minerals (e.g., potassium, calcium, magnesium) modify the association with sodium?
  - b. Among subpopulations defined by sex, race/ethnicity, age (adults, older adults, elderly), and for women (pregnancy and lactation).
  - c. Among subpopulations defined by hypertension, diabetes, obesity and renal health status.

## Potassium

5. Among children and adults what is the **effect** of interventions to increase potassium intake on blood pressure and kidney stone formation?
  - a. Do other minerals (e.g., sodium, calcium, magnesium) modify the effect of potassium?

- b. Among subpopulations defined by sex, race/ethnicity, age (children, adolescents, young adults, older adults, elderly), and for women (pregnancy and lactation).
  - c. Among subpopulations defined by hypertension, diabetes, obesity and renal health status.
- 6. Among children and adults, what is the **association** between potassium intake and blood pressure and kidney stone formation?
  - a. Among subpopulations defined by sex, race/ethnicity, and age (children, adolescents, young adults, older adults, elderly).
  - b. Among subpopulations defined by hypertension, diabetes, and obesity health status.
- 7. Among adults, what is the **effect** of interventions aimed at increasing potassium intake on CVD, and kidney disease morbidity and mortality, and total mortality?
  - a. Do other minerals modify the effect of potassium (e.g., sodium, calcium, magnesium)?
  - b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).
  - c. Among subpopulations defined by hypertension, diabetes, obesity and renal health status.
- 8. Among adults, what is the **association** between dietary potassium intake and CVD, CHD, stroke and kidney disease morbidity and mortality, and between dietary potassium and total mortality?
  - a. Do other minerals (e.g., sodium, calcium, magnesium) modify the association with potassium?
  - b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).
  - c. Among subpopulations defined by hypertension, diabetes, and obesity health status.

### III. Analytic Frameworks

The analytical framework details the population, interventions and exposure, and outcomes of key questions and is a graphical representation of how the key questions are interconnected. This review will utilize two analytic frameworks: one that maps the proposed linkages between sodium intake (as demonstrated by validated indicators) and health effects, and a second that maps the proposed linkages between potassium intake (as demonstrated by validated indicators) and health outcomes.

**Figure 1. Draft analytic framework for sodium and health outcomes**

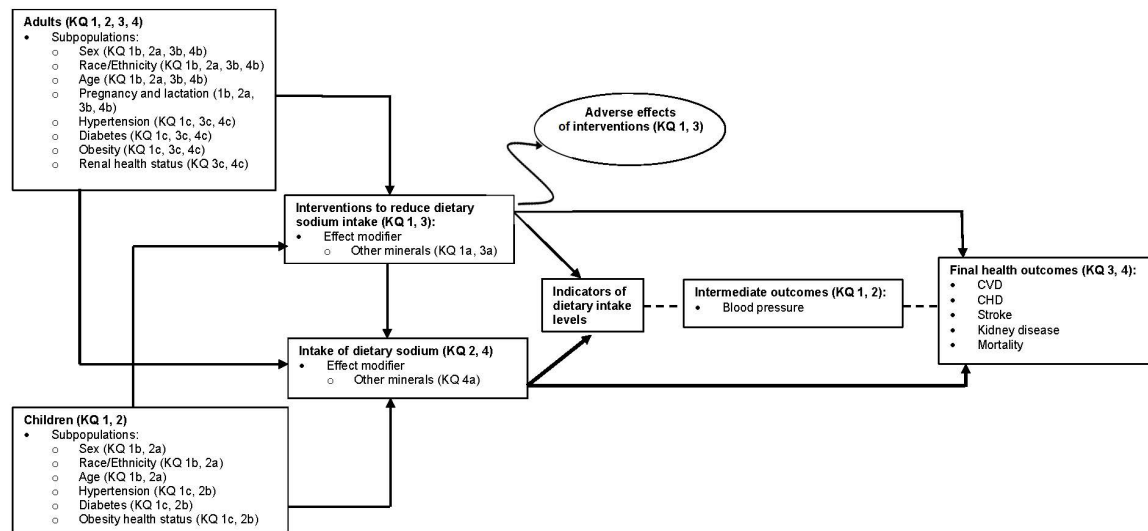


Figure notes: CHD = Coronary Heart Disease; CVD = Cardiovascular Disease; KQ = Key Question

**Figure 2. Draft analytic framework for potassium and health outcomes**

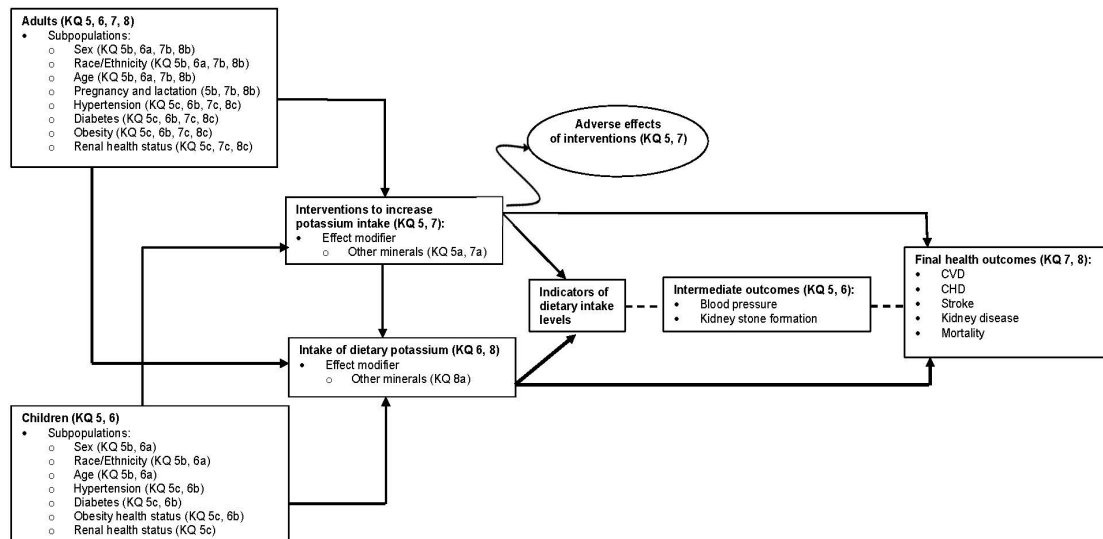


Figure notes: CHD = Coronary Heart Disease; CVD = Cardiovascular Disease; KQ = Key Question

## IV. Methods

The Evidence-based Practice Center (EPC) will conduct this review following established methods as outlined in the Agency for Healthcare Research and Quality (AHRQ)'s Methods Guide for Comparative Effectiveness Reviews.<sup>17</sup>

### A. Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion and exclusion criteria are structured according to the PICOTSS (population, intervention/exposure, comparison group, outcome, time, setting, and study design) framework. The proposed criteria are based on the 2005 IOM report and on discussions



with and recommendations of federal sponsors for the current review. The key questions address the effects of interventions and the strength of association between sodium and potassium intake and health outcomes.

Given the large number of existing intervention studies of sodium reduction and potassium and the suitability and robustness of the RCT design to assess the effect of interventions, we will restrict KQ 1, 3, 5, and 7 to RCTs. Key questions pertaining to the association between sodium and potassium intake and health effects will include observational studies but will be limited to studies that measure and quantify intake with valid indicators to ensure that valid conclusions can be drawn from the identified evidence. Valid assessment measures will be selected together with input from the Technical Expert Panel (TEP) and content expert supporting this systematic review.

The key questions pertaining to associations will exclude studies that exclusively follow participants with preexisting disease specific to the clinical outcome of interest. In order to use valid samples to determine associations, the cohort would need to include participants with and without the condition of interest at follow-up. Because the pool of association studies will include observational studies where the exposure to a specific dietary strategy was self-selected and compared groups may differ in more characteristics than simply dietary sodium or potassium intake, eligible studies will be limited to those reporting baseline data for the outcomes of interest.

The required intervention or exposure duration (e.g., two years for studies on kidney disease) was determined by clinical experts and ensures that only studies will be considered that have sufficient follow-up durations to detect the incident outcome of interest. This evidence review will answer the KQs below using existing, high-quality systematic reviews as a foundation. Given the level of detail needed to evaluate the existing research studies, systematic reviews will not be included in the review in their entirety, but they will be critical to identify the existing relevant primary research, supplementing our literature searches for more recent studies.

Given the complexity of the review, the eligibility criteria are described by key question.

#### **Key Question 1.**

- Population
  - Studies in human participants will be eligible for inclusion in the review, with the exception of studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer.
- Interventions
  - Studies evaluating interventions to reduce dietary sodium intake that specify the oral consumption from food or supplements of quantified amounts of sodium and sodium chloride (salt) or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of +/- 3% or more. Interventions simultaneously addressing sodium and potassium intake that document sodium/potassium ratio are eligible; all other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.
- Comparators

- Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of sodium intake, or studies that alter sodium/potassium ratio in other ways will be included if they control for other nutrient levels.
- Outcomes
  - Studies reporting on blood pressure outcomes (e.g., systolic blood pressure, diastolic blood pressure, rate of hypertensive/non-hypertensive participants, incident hypertension, percent participants at blood pressure goal, and change in blood pressure) will be eligible.
- Timing
  - Studies reporting on an intervention period of at least four weeks will be eligible.
- Setting
  - Studies in outpatient settings will be eligible.
- Study design
  - Parallel RCTs and cross-over RCTs with a washout period of two weeks or more will be eligible.

## **Key Question 2.**

- Population
  - Studies in community-dwelling (non-institutionalized) human participants will be eligible for inclusion in the review with the exception of studies exclusively reporting on patients with pre-existing conditions specific to the clinical outcome of interest, as well as studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer.
- Exposure
  - Studies that measure the intake (oral consumption from food or supplements of quantified amounts of sodium and sodium chloride [salt] or sodium-to-potassium ratio) with validated measures or that use biomarker values to assess sodium level ((at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of salt substitute with intervention/exposure adherence measure, and food diaries with reported validation [adherence check, electronic prompts]) will be eligible. Observational studies that report a weight change of +/- 3% or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies relying only on serum sodium levels, composition of salt substitute without intervention/exposure adherence measure, food diaries without reported validation, use of a published food frequency questionnaire, or partial or spot urine without reported prediction equation will be excluded.
- Comparator
  - Studies comparing groups with different documented sodium intake or biomarker values for sodium will be eligible. Studies where differences in sodium intake or values are confounded with alteration of other nutrient levels will be excluded.



- Outcomes
  - Studies reporting on blood pressure outcomes (e.g., systolic blood pressure, diastolic blood pressure, rate of hypertensive/non-hypertensive participants, incident hypertension, percent participants at blood pressure goal, change in blood pressure) will be eligible. Studies that do not report baseline blood pressure status will be excluded.
- Timing
  - Studies reporting on an intervention period of at least four weeks will be eligible.
- Setting
  - Studies in community-dwelling participants will be eligible.
- Study design
  - Prospective cohort studies and nested case-control studies, where at least two groups are compared based on measured sodium intake or biomarker values will be eligible. Retrospective studies, case series, cross-sectional studies or surveys, and case reports will be excluded.

### **Key Question 3.**

- Population
 

Studies in human adults will be eligible for inclusion in the review. Studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer will be excluded.
- Intervention
  - Studies evaluating interventions to reduce dietary sodium intake that specify the oral consumption from food or supplements of quantified amounts of sodium and sodium chloride (salt) or sodium-to-potassium ratio will be eligible. Studies with trial arms in which participants demonstrate a weight change of  $\pm 3\%$  or more will be excluded. Interventions simultaneously addressing sodium and potassium intake with documents sodium/potassium ratio are eligible. All other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.
- Comparators
  - Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of sodium intake, or studies that alter sodium/potassium ratio in other ways will be included if they control for other nutrient levels.
- Outcomes
  - Studies reporting on mortality (all-cause, CVD, CHD, or renal); cardiovascular disease morbidity, including acute coronary syndrome (unstable angina and myocardial infarction), stroke, myocardial infarction (ST-segment elevation myocardial infarction [STEMI] and non-ST elevation myocardial infarction [NSTEMI]), requiring coronary revascularization procedures (angioplasty, coronary stent placement,

coronary artery bypass), other atherosclerotic revascularization procedures (carotid endarterectomy), left ventricular hypertrophy, hospitalization for heart failure, hospitalization for any cause of coronary heart disease or cardiovascular disease, or combined CVD morbidity and mortality; or reporting on renal function intermediary and clinical outcomes including creatinine clearance (CrCl), serum creatinine (SCr), glomerular filtration rate (GFR), end stage renal disease, chronic kidney disease (CKD), albuminuria or proteinuria (including urine albumin-to-creatinine ratio, urine albumin dipstick level, urine protein-to-creatinine ratio, albumin excretion rate), kidney stone incidence, or acute kidney injury will be eligible.

- Timing
  - Only interventions of two years or longer will be included for kidney disease outcomes; only interventions of three months or longer will be included for cardiovascular disease outcomes; all other studies need to report on an intervention period of at least four weeks to be eligible.
- Setting
  - Studies in outpatient settings will be eligible.
- Study design
  - Parallel RCTs and cross-over RCTs with a washout period of two weeks or more will be eligible.

#### **Key Question 4.**

- Population
  - Studies in community-dwelling (non-institutionalized) adults will be eligible for inclusion in the review with the exception of studies exclusively reporting on patients with pre-existing conditions specific to the clinical outcomes of interest, as well as studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer.
- Exposure
  - Studies that measure the intake (oral consumption from food or supplements of quantified amounts of sodium and sodium chloride [salt] or sodium-to-potassium ratio) with validated measures or use biomarker values to assess sodium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of salt substitute with intervention/exposure adherence measure, and food diaries with reported validation [adherence check, electronic prompts]) will be eligible. Observational studies that report a weight change of +/- 3% or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies relying only on serum sodium levels, composition of salt substitute without intervention/exposure adherence measure, food diaries without reported validation, use of a published food frequency questionnaire, or partial or spot urine without reported prediction equation will be excluded.
- Comparator

- Studies comparing groups with different documented sodium intake or biomarker values for sodium will be eligible. Studies where differences in sodium intake or values are confounded with alteration of other nutrient levels will be excluded.
- Outcomes
  - Studies reporting on mortality (all-cause, CVD, CHD, or renal); cardiovascular mortality; cardiovascular disease morbidity, including coronary heart disease (CHD), acute coronary syndrome (unstable angina and myocardial infarction), stroke, myocardial infarction (ST-segment elevation myocardial infarction [STEMI] and non-ST elevation myocardial infarction [NSTEMI]), requiring coronary revascularization procedures (angioplasty, coronary stent placement, coronary artery bypass), other atherosclerotic revascularization procedures (carotid endarterectomy), left ventricular hypertrophy, hospitalization for heart failure, or hospitalization for any cause of coronary heart disease or cardiovascular disease, or combined CVD morbidity and mortality; or reporting on renal function intermediary and clinical outcomes including creatinine clearance (CrCl), serum creatinine (SCr), glomerular filtration rate (GFR), end stage renal disease, chronic kidney disease (CKD), albuminuria/ proteinuria (including, urine albumin-to-creatinine ratio, urine albumin dipstick level, urine protein-to-creatinine ratio, albumin excretion rate), acute kidney injury will be eligible. Studies that do not report baseline data for the outcomes of interest will be excluded.
- Timing
  - Studies reporting exclusively on kidney disease outcomes need to report follow up periods of at least two years, studies reporting exclusively on cardiovascular disease outcomes or stroke need to report on follow up periods of at least 12 months duration; studies reporting on other outcomes need to evaluate exposure lasting at least four weeks to be eligible.
- Setting
  - Studies in community-dwelling participants will be eligible.
- Study design
  - Prospective cohort studies and nested case-control studies, where at least two groups are compared based on measured sodium intake or biomarker values will be eligible. Retrospective studies, case series, cross-sectional studies or surveys, and case reports will be excluded.

### **Key Question 5.**

- Population
  - Studies in human participants will be eligible for inclusion in the review; studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer will be excluded.
- Interventions
  - Studies evaluating interventions to increase dietary potassium intake that specify the oral consumption from food or supplements of quantified

amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of +/- 3% or more among adults. Interventions simultaneously addressing sodium and potassium intake with documents sodium/potassium ratio are eligible; all other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.

- Comparators
  - Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of potassium intake, or studies that alter sodium/potassium ratio in other ways will be included if they control for other nutrient levels.
- Outcomes
  - Studies reporting on blood pressure outcomes (e.g., systolic blood pressure, diastolic blood pressure, rate of hypertensive/non-hypertensive participants, hypertension incidence, percent participants at blood pressure goal, change in blood pressure) and incident kidney stones or kidney stone regrowth will be eligible.
- Timing
  - Studies reporting exclusively on kidney stone formation need to report on an intervention period of two years; all other studies need to report on an intervention period of at least four weeks to be eligible.
- Setting
  - Studies in outpatient settings will be eligible.
- Study design
  - Parallel RCTs and cross-over RCTs with a washout period of two weeks or more will be eligible.

#### **Key Question 6.**

- Population
  - Studies in community-dwelling (non-institutionalized) human participants will be eligible for inclusion in the review; studies reporting exclusively on patients with pre-existing conditions specific to the clinical outcomes of interest, as well as studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer will be excluded.
- Exposure
  - Studies that measure intake (oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio) with validated measures or use biomarkers values to assess potassium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of potassium supplement with intervention/exposure adherence measure, use of a published food

frequency questionnaire, and food diaries) will be eligible. Observational studies that report a weight change of  $\pm 3\%$  or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies measuring potassium intake by reporting chemical analysis of diet without intervention/exposure adherence measures, composition of potassium supplement without intervention/exposure measure, or serum potassium will be excluded.

- **Comparator**
  - Studies comparing groups with different documented potassium intake, serum potassium levels, or urinary potassium excretion will be eligible. Studies where differences in potassium intake or values are confounded with alteration of other nutrient levels will be excluded.
- **Outcomes**
  - Studies reporting on blood pressure outcomes (e.g., systolic blood pressure, diastolic blood pressure, rate of hypertensive/non-hypertensive participants, hypertension incidence, percent participants at blood pressure goal, change in blood pressure), and kidney stone incident or kidney stone regrowth will be eligible. Studies that do not report baseline blood pressure status and the presence or absence of kidney stones will be excluded.
- **Timing**
  - Studies exclusively reporting on kidney stone formation need to follow participants for at least five years; all other studies need to report on exposure of at least four weeks to be eligible.
- **Setting**
  - Studies in community-dwelling participants will be eligible.
- **Study design**
  - Prospective cohort studies and nested case-control studies, where at least two groups are compared based on measured potassium intake or biomarker values will be eligible. Retrospective studies, case series, cross-sectional studies or surveys, and case reports will be excluded.

#### **Key Question 7.**

- **Population**
- Studies in adults will be eligible for inclusion in the review; studies reporting exclusively on patients with heart failure, end stage renal disease, HIV, or cancer will be excluded.
- **Interventions**
  - Studies evaluating interventions to increase dietary potassium intake that specify the oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of  $\pm 3\%$  or more. Interventions simultaneously addressing sodium and potassium intake with documents sodium/potassium ratio are eligible; all

other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.

- Comparators
  - Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of potassium intake, or studies that alter sodium/potassium ratio in other ways will be included if they control for other nutrient levels.
- Outcomes
  - Studies reporting on mortality (all-cause, CVD, CHD, or renal); cardiovascular disease morbidity, including acute coronary syndrome (unstable angina and myocardial infarction), stroke, myocardial infarction (ST-segment elevation myocardial infarction [STEMI] and non-ST elevation myocardial infarction [NSTEMI]), requiring coronary revascularization procedures (angioplasty, coronary stent placement, coronary artery bypass), other atherosclerotic revascularization procedures (carotid endarterectomy), left ventricular hypertrophy, hospitalization for heart failure, or hospitalization for any cause of coronary heart disease or cardiovascular disease, or combined CVD morbidity and mortality; or reporting on renal function intermediary and clinical outcomes including creatinine clearance (CrCl), serum creatinine (SCr), glomerular filtration rate (GFR), end stage renal disease, chronic kidney disease (CKD), albuminuria or proteinuria (including urine albumin-to-creatinine ratio, urine albumin dipstick level, urine protein-to-creatinine ratio, albumin excretion rate), kidney stone incidence, or acute kidney injury will be eligible.
- Timing
  - Studies reporting exclusively on kidney disease outcomes need to report on an intervention period of two years, studies reporting on cardiovascular disease or stroke need to report on an intervention period of three months; all other studies need to report on an intervention period of at least four weeks to be eligible.
- Setting
  - Studies in outpatient settings will be eligible.
- Study design
  - Parallel RCTs and cross-over RCTs with a washout period of two weeks or more will be eligible.

### **Key Question 8.**

- Population
  - Studies in community-dwelling (non-institutionalized) adults will be eligible for inclusion in the review with the exception of studies exclusively reporting on patients with pre-existing conditions specific to the clinical outcomes of interest, as well as studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer.



- Exposure
  - Studies that measure intake (oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio) with validated measures or use biomarkers values to assess potassium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of potassium supplement with intervention/exposure adherence measure, use of a published food frequency questionnaire, and food diaries) will be eligible. Observational studies that report a weight change of  $\pm 3\%$  or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies measuring potassium intake by reporting chemical analysis of diet without intervention/exposure adherence measures, composition of potassium supplement without intervention/exposure measure, or serum potassium will be excluded.
- Comparator
  - Studies comparing groups with different documented potassium intake, serum potassium levels, or urinary potassium excretion will be eligible. Studies where differences in potassium intake or values are confounded with alteration of other nutrient levels will be excluded.
- Outcomes
  - Studies reporting on mortality (all-cause, CVD, CHD, or renal); cardiovascular disease morbidity, including coronary heart disease (CHD), acute coronary syndrome (unstable angina and myocardial infarction), stroke, myocardial infarction (ST-segment elevation myocardial infarction [STEMI] and non-ST elevation myocardial infarction [NSTEMI]), requiring coronary revascularization procedures (angioplasty, coronary stent placement, coronary artery bypass), other atherosclerotic revascularization procedures (carotid endarterectomy), left ventricular hypertrophy, hospitalization for heart failure, or hospitalization for any cause of coronary heart disease or cardiovascular disease, or combined CVD morbidity and mortality; or reporting on renal function intermediary and clinical outcomes including creatinine clearance (CrCl), serum creatinine (SCr), glomerular filtration rate (GFR), end stage renal disease, chronic kidney disease (CKD), albuminuria/ proteinuria (including urine albumin-to-creatinine ratio, urine albumin dipstick level, urine protein-to-creatinine ratio, albumin excretion rate), kidney stone incidence, or acute kidney injury will be eligible. Studies that do not report baseline data on the outcomes of interest will be excluded.
- Timing
  - Studies reporting exclusively on kidney stone formation need to follow participants for at least five years, studies reporting exclusively on kidney disease need to follow participants for at least two years, studies reporting exclusively on cardiovascular disease or stroke need to follow patients for

at least 12 months; all other studies need to report on an exposure period of at least four weeks to be eligible.

- Setting
  - Studies in community-dwelling participants will be eligible.
- Study design
  - Prospective cohort studies and nested case-control studies, where at least two groups are compared based on measured potassium intake or biomarker values will be eligible. Retrospective studies, case series, cross-sectional studies or surveys, and case reports will be excluded.

### **Other exclusions applying to all key questions:**

Only full-text peer-reviewed English-language publications will be included. Short communications such as conference abstracts cannot fairly be assessed for risk of bias, peer review adds quality control, and the translation of non-English language publications is too resource-intensive for the project given the large volume of research on the topic.

### **B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

We will first complete a scoping review of the existing systematic reviews and evidence reports on sodium and potassium intake, including the 2005 DRI report, to identify critical sources of collated research evidence relevant to this evidence report.

Additional searches will commence with the year 2003, the year during which references were sought for the original DRI report on sodium and potassium. We will develop separate search strategies for each key question (see Appendix B). Searches will be designed and conducted in accordance with the latest edition of the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.<sup>17</sup>

We will conduct literature searches in PubMed, CINAHL, EMBASE, the Cochrane Database of Systematic Reviews (CDSR), CENTRAL, and Web of Science for English-language publications. In addition, reference lists of the existing systematic reviews on the outcomes of interest will be screened to identify relevant studies.

Pairs of reviewers, including at least one senior, experienced reviewer, will independently screen all citations found by literature searches. Upon the start of citation screening, we will implement a training session where all literature reviewers screen the same citations and conflicts will be discussed. We will iteratively continue training until we have reached reasonable inter-rater reliability. For all citations that are deemed potentially relevant by at least one reviewer, full-text publications will be retrieved. Full-text publications will be independently screened by two reviewers, applying the inclusion and exclusion criteria. Disagreements will be resolved through discussion in the review team and the reason for exclusion will be recorded.

We will use online software (DistillerSR®) to manage literature search outputs, screening, and data abstraction.

### **C. Data Abstraction and Data Management**

A detailed and standardized data extraction form will be used to record study-level information (and risk of bias assessments) for all studies meeting inclusion criteria. The form will be pilot-tested and refined within the review team. Data will be extracted by one reviewer and checked by a second, senior systematic reviewer to ensure accuracy. Outcome data, including confounders and effect modifiers) will be abstracted and prepared for analysis by a biostatistician. We will re-extract data from studies included in the 2005 report and identified through other systematic reviews that meet inclusion criteria to enable a comprehensive overview of the existing evidence base to answer the key questions.

All included studies will be documented in comprehensive evidence tables in the report. At the end of the project, all data will be uploaded to customized forms in Systematic Review Data Repository (SRDR) online system (<http://srdp.ahrq.gov>) for full public access.

#### **Data abstraction variables**

- Study details
  - ID, country, study design, sample size by intervention/exposure group, trial name, number of study sites, start and end years of studies (where reported)
- Population
  - Age range or mean age, sex, race/ethnicity, comorbidities (baseline BMI, baseline blood pressure, chronic disease status [CVD, type 2 diabetes, kidney disease, history of kidney stones] [KQ5-8]), inclusion and exclusion criteria
  - Presence of subgroup analyses on prespecified subgroups of interest (see synthesis section for details)
- Interventions (KQ1, 3, 5, 7)
  - Type of intervention; description of sodium, potassium, and sodium/potassium ratio intended intake and form of administration, measure of sodium or potassium status, calcium and magnesium intake, presence of other minerals, washout duration
- Exposure (KQ2, 4, 6, 8)
  - Type of dietary intake, level of sodium, level of potassium, level of sodium/potassium ratio, measure of sodium or potassium status, other minerals
- Comparator
  - Type and description of comparator
- Outcomes

- Method(s) used to assess outcomes; adjusted confounders in non-randomized studies;
- Results at the latest follow-up for KQ1, 2, 5, 6 as reported by study authors
  - Systolic blood pressure, diastolic blood pressure, percent participants at blood pressure goal, hypertension incidence (for KQ1 also at the time of the intervention)
    - In included studies not reporting on the prespecified outcomes: one study-specific blood pressure measure
  - Number of patients with kidney stones (occurrence and recurrence, symptomatic and asymptomatic), kidney stone incidence, number of kidney stones, symptomatic kidney stone incidence (for KQ5, 6 only)
    - In included studies not reporting on the prespecified outcomes: one kidney stone measure (other kidney stone results)
  - Potential adverse events associated with sodium or potassium intake (dizziness, hyperkalemia, glucose intolerance, changes in blood lipids, hyponatremia, fatigue, nausea or vomiting, changes in catecholamine levels and renin/angiotensin/aldosterone)
  - Potential adverse events associated with adherence to diet (e.g., decreased quality of life)
- Results at the latest follow up for KQ3, 4, 7, 8 as reported by study authors
  - All-cause mortality, CVD mortality, CHD mortality, renal disease mortality
  - Stroke, coronary heart disease, myocardial infarction
  - Number of patients with any CVD event as reported by the study authors together with the definition; combined CHD morbidity/mortality and combined CVD morbidity/mortality (using the following prioritization: if a study reports more than one outcome in this category, we will abstract data for only one type of event; hierarchy: combined fatal and nonfatal events, fatal events, nonfatal events)
  - In included studies not reporting on the prespecified CVD outcomes: one CVD measure (e.g., number of patients requiring coronary revascularization procedures)
  - Mean difference between groups in eGFR, number of patients with end stage renal disease
  - In included studies not reporting on the prespecified outcomes: one renal function measure (e.g., urine albumin/creatinine ratio)

- (UACR), serum creatinine, albumin excretion, albuminuria, chronic kidney disease, creatinine clearance, or other)
  - Potential adverse events associated with sodium or potassium intake (dizziness, hyperkalemia, glucose intolerance, changes in blood lipids, hyponatremia, fatigue, nausea or vomiting, changes in catecholamine levels and renin/angiotensin/aldosterone)
  - Potential adverse events associated with adherence to diet (e.g., decreased quality of life)
- Timing
  - Intervention or exposure duration, time between end of intervention or exposure to follow up measurement

#### **D. Assessment of Methodological Risk of Bias of Individual Studies**

We will assess the methodological risk of bias of each original study included in the review, based on predefined criteria. We will implement the Cochrane Risk of Bias tool to assess risk of bias of RCTs and use questions relevant for prospective studies from the Newcastle-Ottawa tool to assess risk of bias among observational studies.<sup>18, 19</sup>

The Cochrane Risk of Bias tool assesses selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The risk of bias and confounding domains for non-randomized studies will address the selection of study cohorts, the compatibility of cohorts, and the assessment of outcomes. Other sources of bias that will be considered are the funding source and potential conflict of interest, length of washout period for cross-over trials, potential for systematic error (e.g., instructed reduction of intake without validation or use of dietary intake measure only) and random error in sodium assessment (e.g., less than 24-hour urine collection or single day dietary recall), and methods to assure adherence to dietary interventions.

One reviewer will assess the methodological risk of bias for all included studies and at least one other reviewer will confirm or refute the risk of bias assessments. Disagreement will be discussed among the systematic review team and resolved via group consensus. The risk of bias assessment process will be designed in consultation with the TEP. When determining the overall strength of evidence, we will consider any quality issues pertinent to the specific outcomes of interest.

Systematic reviews that are included in the review as sources of data will have the risk of bias of their included studies assessed using the appropriate assessment tool. If the systematic review has assessed the risk of bias for included studies using the Cochrane or Newcastle Ottawa method, we will assess risk of bias of a small sample of their included studies to ascertain agreement; if their assessments are in general agreement with ours, we will accept their overall assessments of risk of bias. If disagreement exists or if no risk of bias assessment was conducted, we will assess all included studies.<sup>20</sup> Original studies that are reference mined from existing systematic reviews will be screened, assessed for risk-of-bias, and data abstracted along with studies identified in literature searches.

## E. Data Synthesis

All included studies will be presented in detailed evidence tables to enable a comprehensive overview of the existing evidence base. Continuous outcomes will be reported as standardized mean differences (SMD), dichotomous incident and prevalence outcomes will be reported as relative risks (RR), and mortality data will be reported as hazard ratios (HR), all together with the 95% confidence interval (CI).

Meta-analysis will be used to synthesize results across studies in random effect models. The decision to statistically pool original studies will be based on enrollment of similar populations or subpopulations (based on baseline comorbidities and nutrient status), implementation of similar interventions or use of similar exposure measures, and use of compatible outcome measures. Studies including patients with pre-existing conditions specific to the clinical outcome of interest will be excluded from analyses for the respective outcome of interest in this review, unless they report subgroup data where patients with pre-existing conditions were excluded.

We expect that the ranges of intake levels will be highly variable across observational studies. Naïve “high versus low” or extreme quantile meta-analyses may produce uninterpretable pooled results because the ranges of highest and lowest quantile categories of sodium or potassium intake vary substantially across studies. Therefore, when data are sufficient, we will perform both linear and non-linear dose-response meta-regressions to examine the associations between dietary intake levels and the risks of clinical outcomes using a two-stage hierarchical regression model.<sup>21, 22</sup>

Additionally, meta-regressions will assess whether other minerals affect outcomes of interest (KQ1a, 3a, 5a, 7a).

We will conduct and report on subgroup analyses to answer the subquestions on subpopulations of interest, i.e., gender, race/ethnicity, DRI age group(s) where available, and reproductive status (pregnant and lactating women). The DRI age groups include the following: 1-3 y, 4-8y, 9-13y, 14-18y, 19-30y, 31-50y, 51-70y, and  $\geq 71$  y. We will also report on subpopulations defined by hypertension, diabetes, obesity, and renal health status for individual key questions as specified above.

The evidence tables will indicate for all included studies whether data for subgroups of interest are available.

Statistical heterogeneity will be assessed and expressed as the  $I^2$  statistic and considered in interpreting and weighing the results of meta-analyses.

Summary of findings tables organized by key question, interventions or exposures, and key outcomes, will summarize the review questions summarizing the available evidence.

## F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will assess the strength of evidence for key outcomes, based on guidance provided in the AHRQ EPC Methods Guide. The following table lists key outcomes for inclusion in the SOE assessment; the final determination of which outcomes to include was made with TEP input. The same outcomes used to answer the eight key questions will be used to answer the 12 subquestions.



Table. Outcomes for Determination of Strength of Evidence (SoE)

Key question	Key Outcomes
KQ1.	Mean difference in systolic BP Mean difference in diastolic BP Percent participants at blood pressure goal Hypertension incidence Adverse events associated with sodium intake
KQ2.	Mean difference in systolic BP Mean difference in diastolic BP Percent participants at blood pressure goal Hypertension incidence
KQ3.	All-cause mortality CVD mortality CHD mortality Renal disease mortality Stroke Coronary heart disease Myocardial infarction Number of patients with any CVD event as reported by the study authors Combined CHD morbidity/mortality Combined CVD morbidity/mortality Mean difference between groups in eGFR Number of patients with end stage renal disease Adverse events associated with sodium intake
KQ4.	All-cause mortality CVD mortality CHD mortality Renal disease mortality Stroke Coronary heart disease Myocardial infarction Number of patients with any CVD event as reported by the study authors Combined CHD morbidity/mortality Combined CVD morbidity/mortality Mean difference between groups in eGFR Number of patients with end stage renal disease
KQ5.	Mean difference systolic BP Mean difference in diastolic BP Percent participants at blood pressure goal Hypertension incidence Number of patients with kidney stones (occurrence and recurrence, symptomatic and asymptomatic) Kidney stone incidence Number of kidney stones Symptomatic kidney stone incidence Hyperkalemia
KQ6.	Mean difference systolic BP Mean difference in diastolic BP Percent participants at blood pressure goal Hypertension incidence Number of patients with kidney stones (occurrence and recurrence,

Key question	Key Outcomes
	symptomatic and asymptomatic) Kidney stone incidence Number of kidney stones Symptomatic kidney stone incidence
KQ7.	All-cause mortality CVD mortality CHD mortality Renal disease mortality Stroke Coronary heart disease Myocardial infarction Number of patients with any CVD event as reported by the study authors Combined CHD morbidity/mortality Combined CVD morbidity/mortality Mean difference between groups in eGFR Number of patients with end stage renal disease Hyperkalemia
KQ8.	All-cause mortality CVD mortality CHD mortality Renal disease mortality Stroke Coronary heart disease Myocardial infarction Number of patients with any CVD event as reported by the study authors Combined CHD morbidity/mortality Combined CVD morbidity/mortality Mean difference between groups in eGFR Number of patients with end stage renal disease

The SOE approach assesses the body of evidence for each conclusion based on five dimensions: study limitations (the risk of bias of the individual studies and the study designs), consistency (the degree to which included studies find the same direction or similar magnitude of effect, within and across study designs), directness (i.e., of study outcome measures, that is, whether the outcome in question is intermediary or clinical), precision (the degree of certainty surrounding an effect estimate), and reporting bias (the likelihood that some findings were omitted from publication).

Four strength-of-evidence ratings will be used—high, moderate, low, or insufficient—as defined below. Bodies of evidence based entirely on pooled RCTs are considered to have a high strength of evidence, which can be down-graded for major concerns in each of the domains (study limitations, indirectness, inconsistency, imprecision, or suspected reporting bias). For a body of evidence that includes both RCTs and observational studies, if the RCT evidence is robust, observational studies may not contribute to strengthening the evidence unless they are high quality studies with large, precise effect sizes. Similarly, because of challenges in accounting for confounding, a body of evidence comprising only observational studies usually can provide only a low strength of

evidence unless the studies demonstrate a very large effect, a strong dose-response association, or the observed effect cannot be accounted for by uncontrolled confounding.

### Definitions of the Levels of Strength of Evidence<sup>23</sup>

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion

### G. Assessing Applicability

Applicability will be assessed at the level of the total body of evidence for each conclusion. We will consider the similarity of the population to the North American population in terms of mean baseline intakes/status of sodium and potassium, weight status, and baseline comorbidities, as well as age.

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## VI. Definition of Terms

Not applicable

## VII. Summary of Protocol Amendments

[[If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:



Date	Section	Original Protocol	Revised Protocol	Rationale
3/1/17	B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions Paragraph 2	“Additional searches will be conducted for more recent literature. Searches will commence with the year of completion of the searches conducted for high-quality systematic reviews that we identify that match the inclusion criteria for this review.”	“Additional searches will commence with the year 2003, the year during which references were sought for the original DRI report on sodium and potassium.”	At the request of the co-sponsors, the entire body of literature dating from the year prior to publication of the original DRI report will be systematically searched for studies of potential relevance, rather than relying on prior systematic reviews to identify studies published prior to 2011.
3/1/17	<b>Appendix A.</b> Preliminary Literature Search Strategy	<b>DATABASE SEARCHED &amp; TIME PERIOD COVERED:</b> PubMed – 1/1/2011 – present (searched 3 October 2016)	<b>DATABASE SEARCHED &amp; TIME PERIOD COVERED:</b> PubMed – 1/1/2003 – present (searched 2 March 2017)	Same rationale as above; number of results also revised for each search
3/26/17	<b>VIII. Review of Key Questions</b>	[[AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.]]	The Key Questions were provided in the original scope of work and were refined after input from the Technical Expert Panel (TEP) and from the partners. This input is intended to ensure that the key questions are specific and relevant.	The language that was in that section was from the original template. We have revised the language to reflect how the key questions were reviewed.
3/26/17	XIII. Role of the Funder	This project was funded under Contract No. xxx-xx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services.	This project was funded under Contract No. HHSA290201500010I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services.	Added the contract number

(NOTE THE FOLLOWING PROTOCOL ELEMENTS ARE STANDARD SECTIONS TO BE ADDED TO ALL PROTOCOLS)]

### VIII. Review of Key Questions

[[AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.]]

### X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

### XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.]]

### XII. EPC Team Disclosures

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None of the EPC team members has any conflict of interest. EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

### XIII. Role of the Funder

[[This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.]]

## IV. Appendices

### **Appendix A. Preliminary Literature Search Strategy**

#### **KQ1 Effects of interventions to reduce sodium intake on blood pressure**

##### **DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 1/1/2003 – present (searched 2 March 2017)

##### **LANGUAGE:**

English

##### **SEARCH STRATEGY:**

((("Sodium Chloride"[Mesh] OR "Sodium Glutamate"[Mesh] OR "monosodium glutamate"[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract] OR intake[Text Word] OR "urinary excretion") OR "Diet, Sodium-Restricted"[Mesh] OR "Sodium, Dietary"[Mesh]) AND ("Blood Pressure"[Mesh] OR "blood pressure" OR hypertens\*) AND humans[MESH] OR ((inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb ] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti])) AND (random\* OR randomized controlled trial[pt] OR randomized controlled trials OR rct\* OR blind\* OR double-blind\* OR single-blind \*)))

**Results: 892-dups with SRS=793**

##### **NUMBER OF RESULTS: 1282**

Plus reference mining Aburto et al., 2013<sup>24</sup>, Johnson et al., 2015<sup>25</sup>; He et al., 2013<sup>26</sup>; Peng et al., 2014<sup>27</sup>; Graudal et al., (2012)<sup>28</sup>; Graudal et al. (1998)<sup>29</sup>; DRI report; and other systematic reviews identified in the scoping search

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#### **KQ2 Association between sodium intake and blood pressure**

##### **DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 1/1/2003 – present (searched 2 March 2017 )

##### **LANGUAGE:**

English

##### **SEARCH STRATEGY:**

((("Sodium Chloride"[Mesh] OR "Sodium Glutamate"[Mesh] OR "monosodium glutamate"[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract] OR intake[Text Word] OR "urinary excretion") OR "Diet, Sodium-Restricted"[Mesh] OR "Sodium, Dietary"[Mesh]) AND "Blood Pressure"[Mesh] OR "blood pressure" OR hypertens\* AND "Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh:NoExp] OR "prospective cohort" OR "nested case-control" OR "metabolic study" OR experiment\*[tiab] OR clinical trial\* AND humans[MESH] OR ((inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb ] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti])))

**NUMBER OF RESULTS: 891 – duplicates = 583**

Plus reference mining Aburto et al., 2013<sup>24</sup>, Johnson et al., 2015<sup>25</sup>; DRI report and other systematic reviews identified in the scoping search

### **KQ3 Effects of interventions to reduce sodium intake on cardiovascular disease, kidney disease, and mortality**

#### **DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 1/1/2003 – present (searched 2 March 2017)

#### **LANGUAGE:**

English

#### **SEARCH STRATEGY:**

((("Sodium Chloride"[Mesh] OR "Sodium Glutamate"[Mesh] OR "monosodium glutamate"[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract] OR intake[Text Word] OR "urinary excretion") OR "Diet, Sodium-Restricted"[Mesh] OR "Sodium, Dietary"[Mesh]) AND "Mortality"[Mesh] OR mortality[sh] OR mortality[tiab] OR "Cardiovascular Diseases"[Mesh] OR "Kidney Diseases"[Mesh] OR cardiovascular disease\*[tiab] OR acute coronary syndrome\*[tiab] OR "unstable angina" OR myocardial infarct\* OR stroke OR strokes OR "heart failure" OR "coronary heart disease" OR renal function\* OR kidney disease\*[tiab] OR "end stage kidney disease"[tiab] OR "creatinine clearance" OR "serum creatinine" OR albuminuria OR proteinuria OR "glomerular filtration" OR chronic kidney disease\*[tiab] OR "albumin-to-creatinine ratio" OR "albumin to

creatinine ratio" OR kidney calculi OR kidney stone\* OR renal lithiasis OR nephrolith\* OR nephrolithiasis OR renal stone OR renal calculi OR acute kidney injur\*  
 AND  
 humans[MESH] OR ((inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb ] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti]))  
 AND  
 (random\* OR randomized controlled trial[pt] OR randomized controlled trials OR rct\* OR blind\* OR double-blind\* OR single-blind \*))

**NUMBER OF RESULTS: 955 – duplicates = 240**

Plus reference mining Aburto et al., 2013<sup>24</sup>; Adler et al., 2014<sup>30</sup>; Johnson et al., 2015<sup>25</sup>; McMahon et al., 2015<sup>31</sup>; Poggio et al., 2015<sup>32</sup>; Graudal et al., 2014<sup>33</sup>; Suckling et al., 2010<sup>34</sup>; Stazzullo et al., 2009<sup>35</sup>; DRI report; and other systematic reviews identified in the scoping search

#### **KQ4 Association between sodium intake and cardiovascular disease, coronary heart disease, stroke, kidney disease, or mortality**

##### **DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 1/1/2003 – present (searched 2 March 2017)

##### **LANGUAGE:**

English

##### **SEARCH STRATEGY:**

((("Sodium Chloride"[Mesh] OR "Sodium Glutamate"[Mesh] OR "monosodium glutamate"[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract] OR intake[Text Word] OR "urinary excretion") OR "Diet, Sodium-Restricted"[Mesh] OR "Sodium, Dietary"[Mesh])  
 AND  
 "Cardiovascular Diseases"[Mesh] OR cardiovascular disease\*[tiab] OR acute coronary syndrome\* [tiab] OR "unstable angina" OR myocardial infarct\* OR stroke OR strokes OR "heart failure" OR "coronary heart disease" OR renal function\* OR kidney disease\*[tiab] OR "creatinine clearance" OR "serum creatinine" OR albuminuria OR proteinuria OR "glomerular filtration" OR "end stage kidney disease"[tiab] OR "Kidney Diseases"[Mesh] OR chronic kidney disease\*[tiab] OR "albumin-to-creatinine ratio" OR "albumin to creatinine ratio" OR kidney stone\* OR acute kidney injur\* OR "kidney calculi" OR renal lithiasis OR nephrolith\* OR nephrolithiasis OR renal stone OR renal calculi OR "Mortality"[Mesh] OR mortality[sh] OR mortality[tiab]  
 AND



"Prospective Studies"[Mesh]) OR "Case-Control Studies"[Mesh:NoExp] OR  
"prospective cohort" OR "nested case-control" OR "metabolic study" OR  
experiment\*[tiab] OR clinical trial\*  
AND  
humans[MESH] OR ((inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb]) NOT  
(mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti]))

**NUMBER OF RESULTS: 1086 – duplicates = 259**

Plus reference mining Aburto et al., 2013<sup>24</sup>, Johnson et al., 2015<sup>25</sup>; McMahon et al.,  
2015<sup>31</sup>; Poggio et al., 2015<sup>32</sup>; Graudal et al., 2014<sup>33</sup>; Suckling et al., 2010<sup>34</sup>; Strazzullo et  
al., 2009<sup>35</sup> Adler et al., 2014<sup>30</sup>; DRI report; and other systematic reviews identified in the  
scoping search

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### **KQ5 Effect of interventions to increase potassium intake on blood pressure and kidney stone formation**

#### **DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 1/1/2003 – present (searched 2 March 2017)

#### **LANGUAGE:**

English

"Potassium, Dietary"[Mesh] OR potassium[tiab] OR KIOR-CON[tiab] OR KCL[tiab]  
AND  
"Blood Pressure"[Mesh] OR "blood pressure" OR hypertens\* OR kidney calculi OR  
kidney stone\* OR renal lithiasis OR nephrolith\* OR nephrolithiasis OR renal stone OR  
renal calculi  
AND  
humans[MESH] OR ((inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] ) NOT  
(mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti]))  
AND  
(random\* OR randomized controlled trial[pt] OR randomized controlled trials OR rct\*  
OR blind\* OR double-blind\* OR single-blind \*)

**NUMBER OF RESULTS: 655 – duplicates = 410**

Plus reference mining Aburto et al., 2013<sup>36</sup>; Phillips et al., 2015<sup>37</sup>, NHLBI, 2013<sup>5</sup>; DRI  
report; and other systematic reviews identified in the scoping search

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### **KQ6 Association between potassium intake and blood pressure and kidney stone formation**

#### **DATABASE SEARCHED & TIME PERIOD COVERED:**

Source: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)

Published online: February 1, 2017; updated March 24 and April 18, 2017

PubMed – 1/1/2003 – present (searched 2 March 2017)

**LANGUAGE:**

English

**SEARCH STRATEGY:**

"Potassium, Dietary"[Mesh] OR potassium[tiab] OR Klor-Con[tiab] OR KCL[tiab]  
AND

"Blood Pressure"[Mesh] OR "blood pressure" OR hypertens\* OR kidney calculi OR  
kidney stone\* OR renal lithiasis OR nephrolith\* OR nephrolithiasis OR renal stone OR  
renal calculi

AND

"Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh:NoExp] OR  
"prospective cohort" OR "nested case-control" OR "metabolic study" OR  
experiment\*[tiab] OR clinical trial\*

AND

humans[MESH] OR ((inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb]) NOT  
(mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti]))

**NUMBER OF RESULTS: 748 – duplicates = 382**

Plus reference mining Aburto et al., 2013<sup>36</sup>; Phillips et al., 2015<sup>37</sup>, NHLBI, 2013<sup>5</sup>; DRI  
report; and other systematic reviews identified in the scoping search

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**KQ7 Effects of interventions to increase potassium intake on cardiovascular disease,  
kidney disease, and mortality**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 1/1/2003 – present (searched 2 March 2017)

**LANGUAGE:**

English

"Potassium, Dietary"[Mesh] OR potassium [tiab] OR Klor-Con[tiab] OR KCL[tiab]  
AND

"Mortality"[Mesh] OR mortality[sh] OR mortality[tiab] OR "Cardiovascular  
Diseases"[Mesh] OR "Kidney Diseases"[Mesh] OR cardiovascular disease\*[tiab] OR  
acute coronary syndrome\*[tiab] OR "unstable angina" OR myocardial infarct\* OR stroke  
OR strokes OR "heart failure" OR "coronary heart disease" OR renal function\* OR  
kidney disease\*[tiab] OR "creatinine clearance" OR "serum creatinine" OR albuminuria  
OR proteinuria OR "glomerular filtration" OR "end stage kidney disease"[tiab] OR  
chronic kidney disease\*[tiab] OR "albumin-to-creatinine ratio" OR "albumin to  
creatinine ratio" OR acute kidney injur\* OR kidney calculi OR kidney stone\* OR renal  
lithiasis OR nephrolith\* OR nephrolithiasis OR renal stone OR renal calculi

AND

humans[MESH] OR ((inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti])) AND (random\* OR randomized controlled trial[pt] OR randomized controlled trials OR rct\* OR blind\* OR double-blind\* OR single-blind \*))

**NUMBER OF RESULTS: 1017 – duplicates = 450**

Plus reference mining Aburto et al., 2013<sup>36</sup>; Dickinson et al., 2006<sup>38</sup>; NHLBI, 2013<sup>5</sup>; DRI report; and other systematic reviews identified in the scoping search

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### **KQ8 Association between dietary potassium intake and cardiovascular disease, coronary heart disease, stroke, kidney disease, and mortality**

#### **DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 1/1/2003 – present (searched 2 March 2017)

#### **LANGUAGE:**

English

#### **SEARCH STRATEGY:**

"Potassium, Dietary"[Mesh] OR potassium[tiab] OR Klor-con[tiab] OR KCL[tiab] AND

"Cardiovascular Diseases"[Mesh] OR cardiovascular disease\*[tiab] OR acute coronary syndrome\* [tiab] OR "unstable angina" OR myocardial infarct\* OR stroke OR strokes OR "heart failure" OR "coronary heart disease" OR renal function\* OR kidney disease\*[tiab] OR "creatinine clearance" OR "serum creatinine" OR albuminuria OR proteinuria OR "glomerular filtration" OR "end stage kidney disease"[tiab] OR "Kidney Diseases"[Mesh] OR chronic kidney disease\*[tiab] OR "albumin-to-creatinine ratio" OR "albumin to creatinine ratio" OR kidney stone\* OR acute kidney injury\* OR "kidney calculi" OR renal lithiasis OR nephrolith\* OR nephrolithiasis OR renal stone OR renal calculi OR "Mortality"[Mesh] OR mortality[sh] OR mortality[tiab]

AND

"Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh:NoExp] OR "prospective cohort" OR "nested case-control" OR "metabolic study" OR experiment\*[tiab] OR clinical trial\*

AND

humans[MESH] OR ((inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb]) NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti]))

**NUMBER OF RESULTS: 1594 – duplicates = 736**

Plus reference mining Aburto et al., 2013<sup>36</sup>; Dickinson et al., 2006<sup>38</sup>; NHLBI, 2013<sup>5</sup>; Beyer et al., 2006<sup>39</sup>; DRI report; and other systematic reviews identified in the scoping search

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## Appendix C. Draft Evidence Table

<b>ID</b> <b>Location Country</b> <b>Study Design</b> <b>Trial Name</b> <b>Number of sites</b>	<b>Number Participants</b> <b>% male</b> <b>Mean age, Age range</b> <b>Race/ ethnicity</b> <b>Comorbidities</b> <b>Inclusion/Exclusion criteria</b>	<b>Intervention description</b> <b>Dietary intake</b> <b>Comparator description</b> <b>Duration</b> <b>Follow up</b>	<b>Intake/Status ascertainment</b> <b>Outcome measures</b> <b>Adjustment factors</b>	<b>Findings - Outcomes and comparison</b>
ID: Author name, year Location (Country): e.g., US Design: e.g., post hoc analysis of 2 RCTs Trial Name: e.g., # Sites: Study years:	N per study arm: (N randomized in RCTs) % male: Mean Age: mean, SD Age range: Ethnicity: Race % white Race % black, Race % other Baseline: mean BMI, mean blood pressure, % HTN, % CVD, % T2DM, % kidney disease, % kidney stones Inclusion: list criteria Exclusion: list criteria	Intervention: type (e.g., potassium supplementation); description of diet, form of administration Na intake: g /d, mmol K intake: g /d, mmol Na/K ratio: Other minerals: Comparator: description Duration: duration of intervention/exposure Time between end of exposure and follow up:	Measure and status: e.g., mean/median 24-h urinary excretion , status Outcomes: type and definition (e.g., any CVD event, including MI, stroke, CABG, PTCA, CVD mortality, total mortality) Adjustment factors for observational studies e.g., clinic, treatment assignment, age, sex, race, education, family history, baseline weight, alcohol, smoking, exercise; change in weight, smoking, and exercise	<u>Blood pressure</u> e.g., mean difference (CI) in systolic BP intervention vs control e.g., mean difference (CI) in diastolic BP intervention vs control e.g., RR (CI) patients with hypertension intervention vs control e.g., RR (CI) % reaching prespecified BP goal <u>CVD</u> e.g., RR (CI) any CVD event intervention vs control e.g., RR (CI) stroke intervention vs control e.g., RR (CI) coronary heart disease intervention vs control <u>Renal</u> e.g., HR (CI) kidney disease mortality intervention vs control e.g., mean difference (CI) in eGFR intervention vs control e.g., mean difference in albumin/creatinine ratio intervention vs control e.g., mean difference (CI) in serum creatinine intervention vs control e.g., RR (CI) CKD intervention vs control e.g., RR (CI) ESRD incident intervention vs control e.g., RR (CI) acute kidney injury intervention vs control <u>Kidney stones</u> e.g., RR (CI) kidney stones (incident or recurrent) <u>Mortality</u> e.g., HR (CI) All-cause mortality intervention vs control